

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 May 2006 (04.05.2006)

PCT

(10) International Publication Number
WO 2006/045564 A1

(51) International Patent Classification:
C07D 473/06 (2006.01) *A61K 31/522* (2006.01)
C07D 473/04 (2006.01) *A61P 9/00* (2006.01)

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:
PCT/EP2005/011374

(22) International Filing Date: 20 October 2005 (20.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0423560.2 22 October 2004 (22.10.2004) GB
0427061.7 10 December 2004 (10.12.2004) GB

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

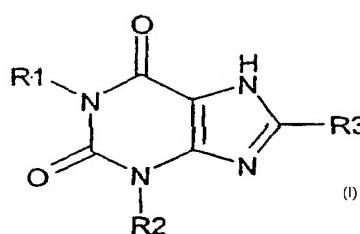
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: XANTHINE DERIVATIVES WITH HM74A RECEPTOR ACTIVITY



(57) Abstract: The present invention relates to therapeutically active compounds of formula (I) which are xanthine derivatives, processes for the manufacture of said derivatives, pharmaceutical formulations containing the active compounds and the use of the compounds in therapy, particularly in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial.

5 The present invention relates to compounds which are xanthine derivatives, processes for the manufacture of said derivatives, pharmaceutical formulations containing the active compounds and the use of the compounds in therapy, particularly in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial.

10 Dyslipidaemia is a general term used to describe individuals with aberrant lipoprotein profiles. Clinically, the main classes of compounds used for the treatment of patients with dyslipidaemia, and therefore at risk of cardiovascular disease are the statins, fibrates, bile-acid binding resins and nicotinic acid. Nicotinic acid (Niacin, a B vitamin) has been used clinically for over 40 years in patients with various forms of dyslipidaemia. The primary mode of action of nicotinic acid is via inhibition of hormone-sensitive triglyceride lipase (HSL),
15 which results in a lowering of plasma non-esterified fatty acids (NEFA) which in turn alters hepatic fat metabolism to reduce the output of LDL and VLDL (low and very low density lipoprotein). Reduced VLDL levels are thought to lower cholesterol ester transfer protein (CETP) activity to result in increased HDL (high density lipoprotein) levels which may be the cause of the observed cardiovascular benefits. Thus, nicotinic acid produces a very
20 desirable alteration in lipoprotein profiles; reducing levels of VLDL and LDL whilst increasing HDL. Nicotinic acid has also been demonstrated to have disease modifying benefits, reducing the progression and increasing the regression of atherosclerotic lesions and reducing the number of cardiovascular events in several trials.

25 The observed inhibition of HSL by nicotinic acid treatment is mediated by a decrease in cellular cyclic adenosine monophosphate (cAMP) caused by the G-protein-mediated inhibition of adenylyl cyclase. Recently, the G-protein coupled receptors HM74 and HM74A have been identified as receptors for nicotinic acid (PCT patent application WO02/84298; Wise et. al. J Biol Chem., 2003, 278 (11), 9869-9874). The DNA sequence of human
30 HM74A may be found in Genbank; accession number AY148884. Two further papers support this discovery, (Tunaru et. al. Nature Medicine, 2003, 9(3), 352-255 and Soga et. al. Biochem Biophys Res Commun., 2003, 303 (1) 364-369), however the nomenclature differs slightly. In the Tunaru paper what they term human HM74 is in fact HM74A and in the Soga paper HM74b is identical to HM74A. Cells transfected to express HM74A and/or HM74 gain
35 the ability to elicit G_i G-protein mediated responses following exposure to nicotinic acid. In mice lacking the homologue of HM74A (m-PUMA-G) nicotinic acid fails to reduce plasma NEFA levels.

40 We now present a group of xanthine derivatives which are selective agonists of the nicotinic acid receptor HM74A and are thus of benefit in the treatment, prophylaxis and suppression of diseases where under-activation of this receptor either contributes to the disease or where activation of the receptor will be beneficial.

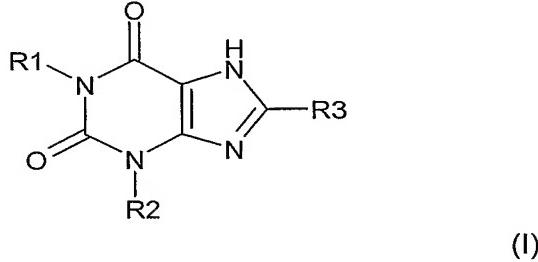
Summary of the Invention

The present invention provides therapeutically active xanthine derivatives and the use of these derivatives in therapy, particularly in the treatment of diseases where under-activation 5 of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial, in particular diseases of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. As such, the compounds may also find favour as therapeutics for 10 coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. The compounds may also be of use in the treatment of inflammatory diseases or conditions, as set out further below.

15 Intermediates, formulations, methods and processes described herein form further aspects of the invention.

Detailed Description of the Invention

20 According to one aspect of this invention we provide at least one chemical entity selected from: compounds of formula (I)



25 and pharmaceutically acceptable derivatives thereof, wherein

R¹ represents a group selected from: hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, and 30 -(alk)_m-X-(alk)_n-Y,

Wherein X represents A, A1, A2 or a direct link;

A represents a group selected from:

35 cycloalkylene, cycloalkenylene, aryl, heteroaryl, heterocyclyl, -CH₂-OC(O)-;

A1 represents a group selected from:

-CH₂-O-(CH₂)_qaryl-O-, -CH₂-O-(CH₂)_wN(R⁵)C(O)O-, -CH₂-N(R⁵)C(O)O-, -CH₂-N(R⁵)C(O)-,

-CH₂-(O)_p-(CH₂)_qC(O)NR⁵-, -CH₂-N(R⁵)C(O)N(R⁵)-, -CH₂-C(O)N((CH₂)_wOH)-,
 -CH₂-NR⁵-S(O)₂-, CH₂-S(O)₂NR⁵-, -CH₂-C(O)O-, -O-, -NR⁵-, -S-;

A2 represents:

5 -CH(OH)-;

When X is A, A1 or A2, Y represents a group selected from:

heteroaryl, heterocyclyl, aryl, cycloalkyl, cycloalkenyl, -O(CH₂)_n-aryl, -C(O)O-aryl, -CH(aryl)₂,
 -CH(heteroaryl)₂, -C₁₋₆ haloalkyl, -C(O)R⁴, -NR⁵R⁷, -C(O)NR⁵R⁷, -NR⁵C(O)R⁷, -NR⁵C(O)OR⁷,
 10 -C(O)(CH₂)_qOR⁴, halogen, cyano, -N(R⁵)C(O)OR⁷, -OC(O)NR⁵R⁶, -NR⁵C(O)R⁸, -OR⁵,
 -OC(O)R⁴;

When X is A1 and Y is selected from:

-O(CH₂)_n-aryl, -O-heteroaryl, -OR⁵, -OC(O)R⁵, -NH-aryl, -OC(O)NR⁵R⁶,

15 n is an integer selected from 2, 3, 4 and 5;

When X is A1 and Y is -CF₃, or when X is A2, n is an integer selected from 1, 2, 3, 4 and 5;

When X is a direct link, Y represents a group selected from:

20 -C(O)(CH₂)_qOR⁵, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl, -heteroaryl, -heterocyclyl,
 -aryl, -cycloalkyl, -cycloalkenyl, -C₁₋₆ haloalkyl, -halo, -cyano, 3 or 4 ring fused system,
 -CH(aryl)₂, -CH(heteroaryl)₂, -OR⁵, -NR⁵R⁷, -NCOOR⁸, -(O)_pC(O)NR⁵R⁶, -NR⁵C(O)R⁸, -OR⁵,
 -(O)_pC(O)R⁴;

25 When Y incorporates a ring, that ring may be optionally substituted by one or more of:

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -NH₂, (CH₂)_q-NR⁵R⁷,
 -(CH₂)_q-(O)_p-(CH₂)_q-N(R⁵)C(O)OR⁸, -(CH₂)_q-N(R⁵)C(O)R⁸, -(CH₂)_q-(O)_p-(CH₂)_q-C(O)NR⁵R⁶,
 -(CH₂)_q-N(R⁵)C(O)N(R⁵)R⁶, -(CH₂)_q-C(O)N((CH₂)_mOH)R⁵, -(CH₂)_q-N(R⁵)-S(O)₂R⁸,
 -CH₂-S(O)₂N(R⁵)R⁶, -C₁₋₆ haloalkyl, -OCF₃, -OCH(F)₂, -OCH₂F, -COOR⁵, -OR⁵,
 30 -(R⁸)_pCN, -S(O)₂R⁹, -(CH₂)_nheteroaryl, -(CH₂)_nheterocyclyl, -(CH₂)_ncycloalkyl,
 -(CH₂)_ncycloalkenyl, -(CH₂)_naryl;

35 R² is selected from: hydrogen; or C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl,
 cycloalkenyl, heterocyclyl, aryl, and heteroaryl, each of which may be optionally substituted
 by one or more of: C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, heterocyclyl, aryl,
 heteroaryl, C₁₋₆ haloalkyl, halogen, -CN, -OR⁴, -(CH₂)_nCOR⁴, -C(O)OR⁴, -OCOR⁴,
 -(CH₂)_nNR⁵R⁶, -(NH)_pCONR⁵R⁶, -OCONR⁵R⁷, and -NHC(O)OR⁷;

40 R³ is selected from: S-C₁₋₆ alkyl, S-C₂₋₆ alkenyl, S-C₂₋₆ alkynyl, S-(CH₂)_nC₃₋₅ cycloalkyl,
 S-(CH₂)_nC₃₋₅ cycloalkenyl, S-(CH₂)_nC₃₋₅ heterocyclyl, S-(CH₂)_nC₅ aryl. S-(CH₂)_nC₅ heteroaryl;

R⁴ is selected from: hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_n cycloalkyl,
 -(CH₂)_n cycloalkenyl, -(CH₂)_n heterocyclyl, -(CH₂)_n aryl, and -(CH₂)_n heteroaryl;

R⁵ and R⁶ are selected from: hydrogen and C₁₋₄ alkyl;

R⁷ is selected from: hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_tcycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_theterocycl, -(CH₂)_taryl, and -(CH₂)_theteroaryl;

5 R⁸ is selected from C₁₋₄ alkyl;

R⁹ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_nheterocycl, -(CH₂)_naryl, and -(CH₂)_nheteroaryl, CN;

10 m represents an integer selected from: 0, 1, 2, 3, 4 and 5;

n represents an integer selected from: 0, 1, 2, 3, 4 and 5;

15 p represents an integer selected from: 0 and 1;

q represents an integer selected from: 0, 1 and 2;

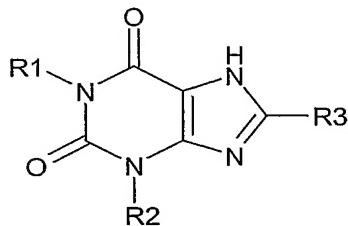
t represents an integer selected from: 1 and 2;

20 w represents an integer selected from: 2, 3 and 4.

with the proviso that:

- 25 i) when R¹ and R² represent ethyl, R³ is other than SMe; and
ii) when R¹ represents ethyl or n-propyl and R² represents n-propyl, R³ is other than SBu-n.

In another aspect of the invention is provided at least one chemical entity selected from:
30 compounds of formula (Ia)



(Ia)

35 and pharmaceutically acceptable derivatives thereof, wherein

R¹ represents hydrogen or a group selected from: C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -(CH₂)_ncycloalkyl, -(CH₂)_nheterocycl, -(CH₂)_naryl and -(CH₂)_nheteroaryl, each of which may be optionally substituted by one or more of: -(CH₂)_ncycloalkyl, -(CH₂)_nheterocycl, -(CH₂)_naryl, -(CH₂)_nheteroaryl, C₁₋₆ haloalkyl, halo, cyano, -OR⁴, -(CH₂)_nCOR⁴, -CO₂R⁴, -OCOR⁴, -(CH₂)_nNR⁵R⁷, -(NH)_mCONR⁵R⁷, -OCONR⁵R⁷, and -NHCO₂R⁷;

R² is selected from: C₂₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, heterocycll, aryl, and heteroaryl, each of which may be optionally substituted by one or more of: cycloalkyl, heterocycll, aryl, heteroaryl, C₁₋₆ haloalkyl, halo, cyano, -OR⁴, -(CH₂)_nCOR⁴, -CO₂R⁴, -OCOR⁴, -(CH₂)_nNR⁵R⁶, -(NH)_mCONR⁵R⁶, -OCONR⁵R⁷, and -NHCO₂R⁷;

5

R³ is selected from: S-C₁₋₁₀alkyl, S-C₂₋₁₀alkenyl, S-C₂₋₁₀alkynyl, S-(CH₂)_ncycloalkyl, S-(CH₂)_nheterocycll, S-(CH₂)_n-aryl, S-(CH₂)_nheteroaryl;

10

R⁴ is selected from: hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_ncycloalkyl, -(CH₂)_nheterocycll, -(CH₂)_naryl, and -(CH₂)_nheteroaryl;

R⁵ and R⁶ are selected from: hydrogen and C₁₋₄ alkyl;

15

R⁷ is selected from: hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_pcycloalkyl, -(CH₂)_pheterocycll, -(CH₂)_paryl, and -(CH₂)_pheteroaryl;

n represents an integer selected from: 0, 1, 2, 3 and 4;

20

m represents an integer selected from: 0 and 1;

p represents an integer selected from: 1 and 2;

with the proviso that:

- 25 i) when R¹ and R² represent ethyl, R³ is other than SMe;
- ii) when R¹ represents ethyl or n-propyl and R² represents n-propyl, R³ is other than SBu-n; and
- 30 iii) when R¹ represents hydrogen and R² represents CH₂-Ph, R³ is other than SCH₂-Ph.

Throughout the present specification and the accompanying claims the words "comprise" and "include" and variations such as "comprises", "comprising", "includes" and "including" are to be interpreted inclusively. That is, these words are intended to convey the possible inclusion of other elements or integers not specifically recited, where the context allows.

As used herein, the terms "halogen" or "halo" refer to fluorine, chlorine, bromine and iodine.

40 As used herein, the term "alkyl" (when used as a group or as part of a group) refers to a straight or branched hydrocarbon chain unless specified otherwise, containing the specified number of carbon atoms. For example, C₃-C₁₀alkyl means a straight or branched hydrocarbon chain containing at least 3 and at most 10 carbon atoms. Examples of alkyl as used herein include, but are not limited to methyl (Me), ethyl (Et), n-propyl and i-propyl.

45 As used herein, the term "alkenyl" refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms which contains one or more double bonds. Suitable examples include but are not limited to ethenyl, 2-propenyl, 3-but enyl, 2-but enyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-but enyl, 3-hexenyl and the like.

As used herein, the term "alkynyl" refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms which contains one or more triple bonds. Suitable examples include but are not limited to acetylenyl, propynyl, 1-butynyl, 1-pentynyl, 3-methyl-1-butynyl and the like.

The term 'C₁₋₆ haloalkyl' as used herein refers to a C₁₋₆ alkyl group as defined herein wherein at least one hydrogen atom is replaced with halogen. Examples of such groups include fluoroethyl, trifluoromethyl or trifluoroethyl and the like.

) As used herein, the term "cycloalkyl" refers to a hydrocarbon ring, containing between 3 and 6 carbon atoms, comprising no heteroatoms or conjugated double bonds. Examples of cycloalkyl as used herein include, but are not limited to cyclopropyl and cyclohexyl.

5) The term 'cycloalkylene' as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon linker groups. Examples of such groups include cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene or cyclooctylene and the like.

) The term 'cycloalkenyl' as used herein refers to an unsaturated non-aromatic monocyclic hydrocarbon ring of 3 to 8 carbon atoms containing one or more carbon-carbon double bonds. Examples of such groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl or cyclooctenyl and the like.

5) The term 'cycloalkenylene' as used herein refers to an unsaturated non-aromatic monocyclic hydrocarbon ring of 3 to 8 carbon linker groups containing one or more carbon-carbon double bonds. Examples of such groups include cyclopropenylene, cyclobutenylene, cyclopentenylene, cyclohexenylene, cycloheptenylene or cyclooctenylene and the like.

) As used herein, the term "aryl" refers to a 5 or 6 membered, monocyclic aromatic group, or a fused 8-10 membered bicyclic aromatic group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. "Aryl" includes carbocyclic aryl and biaryl groups. Suitable examples include but are not limited to phenyl, naphthyl and the like.

5) As used herein, the term "heteroaryl" refers to a 5 or 6 membered, monocyclic aromatic group or a fused 8-10 membered bicyclic, aromatic group containing 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulphur with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. Suitable examples of such monocyclic aromatic rings include but are not limited to thieryl,

) furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include but are not limited to benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl,

indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

- 5 As used herein, the term "heterocyclyl" refers to a 5 or 6 membered, saturated cyclic hydrocarbon group, containing 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulphur. Suitable examples include but are not limited to pyrrolidinyl, morpholinyl, imidazolidinyl and piperazinyl.
- 10 The term '3 or 4 ring fused system' as used herein refers to a fused 12-18 membered tricyclic or tetracyclic ring which contains 1 to 4 heteroatoms of N and wherein at least one ring is aromatic. There may be one or more optional oxo substituents on the ring carbon atoms. Examples of such fused aromatic rings include carbazolyl, acenaphthyl, naphthotriazolyl and the like.
- 15 As used herein, where a group is referred to as being "substituted" by another group or having "one or more substituents" unless a particular position for such a substitution is specified it is to be understood that a substitution may be present at any position in the group.
- 20 As used herein, the term "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example salts, solvates or esters which, upon administration to a mammal, such as a human, are capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles And Practice, which is incorporated herein by reference.
- 25 It will be appreciated by those skilled in the art that the compounds of the invention may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of the invention may be so modified at more than one position.
- 30 In one embodiment, "pharmaceutically acceptable derivative" refers to salts or solvates.
- 35 As used herein, the term "pharmaceutically acceptable" used in relation to an ingredient (active ingredient or excipient) which may be included in a pharmaceutical formulation for administration to a patient, refers to that ingredient being acceptable in the sense of being compatible with any other ingredients present in the pharmaceutical formulation and not being deleterious to the recipient thereof.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I), a salt thereof or a pharmaceutically acceptable derivative thereof) and a solvent. Such solvents for the purposes of the present invention may not interfere with the biological activity of the solute. The solvent used may be a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. An example of a solvent that may be used is water, in which case the solvate may be referred to as a hydrate of the solute in question.

It will be appreciated that, for pharmaceutical use, the "salt or solvate" referred to above will be a pharmaceutically acceptable salt or solvate. However, other salts or solvates may find use, for example, in the preparation of a compound of formula (I) or in the preparation of a pharmaceutically acceptable salt or solvate thereof.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Suitable pharmaceutically acceptable salts include alkali metal salts formed from the addition of alkali metal bases such as alkali metal hydroxides. Examples of suitable alkali metal salts are sodium salt or potassium salt. Other suitable pharmaceutically acceptable salts include alkaline earth metal salts such as calcium salt or magnesium salt, ammonium salts; or salts with organic bases such as ethanolamine, triethanolamine, ethylene diamine, triethylamine, choline and meglumine; or salts with amino acids such as arginine, lysine and histidine.

The compounds are of use in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial, in particular diseases of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such the compounds of the present invention may find use as agonists or partial agonists of HM74A.

Compounds of the invention are of potential therapeutic benefit in the treatment and amelioration of the symptoms of many diseases of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

Furthermore, it is also believed that the HM74 and HM74A receptors are involved in inflammation. Inflammation represents a group of vascular, cellular and neurological responses to trauma. Inflammation can be characterised as the movement of inflammatory cells such as monocytes, neutrophils and granulocytes into the tissues. This is usually associated with reduced endothelial barrier function and oedema into the tissues. Inflammation with regards to disease typically is referred to as chronic inflammation and can last up to a lifetime. Such chronic inflammation may manifest itself through disease symptoms. The aim of anti-inflammatory therapy is therefore to reduce this chronic inflammation and allow for the physiological process of healing and tissue repair to progress.

Examples of inflammatory diseases or conditions for which the compounds of the present invention may demonstrate utility include those of the joint, particularly arthritis (e.g. rheumatoid arthritis, osteoarthritis, prosthetic joint failure), or the gastrointestinal tract (e.g. ulcerative colitis, Crohn's disease, and other inflammatory bowel and gastrointestinal diseases, gastritis and mucosal inflammation resulting from infection, the enteropathy provoked by non-steroidal anti-inflammatory drugs), of the lung (e.g. adult respiratory distress syndrome, asthma, cystic fibrosis, or chronic obstructive pulmonary disease), of the heart (e.g. myocarditis), of nervous tissue (e.g. multiple sclerosis), of the pancreas, (e.g. inflammation associated with diabetes mellitus and complications thereof, of the kidney (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, eczema, urticaria, burn injury), of the eye (e.g. glaucoma) as well as of transplanted organs (e.g. rejection) and multi-organ diseases (e.g. systemic lupus erythematosis, sepsis) and inflammatory sequelae of viral or bacterial infections and inflammatory conditions associated with atherosclerosis and following hypoxic or ischaemic insults (with or without reperfusion), for example in the brain or in ischaemic heart disease.

It will be appreciated that references herein to treatment extend to prophylaxis, prevention of recurrence and suppression of symptoms as well as the treatment of established conditions.

Nicotinic acid has a significant side effect profile, possibly because it is dosed at high level (gram quantities daily). The most common side effect is an intense cutaneous flushing. In certain embodiments of the present invention the compounds may exhibit reduced side effects compared to nicotinic acid. HM74A has been identified as a high affinity receptor for nicotinic acid whilst HM74 is a lower affinity receptor. The compounds of the present invention may find use as selective HM74A agonists or partial agonists; in which case they will show greater affinity for HM74A than for HM74.

The potential for compounds of formula (I) to activate HM74A may be demonstrated, for example, using the following in vitro whole cell assays:

In-vitro testing

For transient transfections, HEK293T cells (HEK293 cells stably expressing the SV40 large T-antigen) were maintained in DMEM containing 10% foetal calf serum and 2mM glutamine.

5 Cells were seeded in 90mm culture dishes and grown to 60-80% confluence (18-24h) prior to transfection. Human HM74A (GenBank™ accession number AY148884) was subcloned in to a mammalian expression vector (pcDNA3; Invitrogen) and transfected using Lipofectamine reagent. For transfection, 9µg of DNA was mixed with 30µl Lipofectamine in 0.6ml of Opti-MEM (Life Technologies Inc.) and was incubated at room temperature for 10 30min prior to the addition of 1.6ml of Opti-MEM. Cells were exposed to the Lipofectamine/DNA mixture for 5h and 6ml of 20% (v/v) foetal calf serum in DMEM was then added. Cells were harvested 48h after transfection. Pertussis toxin treatment was carried out by supplementation into media at 50ng/ml⁻¹ for 16h. All transient transfection studies involved co-transfection of receptor together with the G_{i/o} G protein, G_{o1α}.

15 For generation of stable cell lines the above method was used to transfect CHO-K1 cells seeded in six well dishes grown to 30% confluence. These cells were maintained in DMEM F-12 HAM media containing 10% foetal calf serum and 2mM glutamine. 48h post-transfection the media was supplemented with 400µg/ml Geneticin (G418, Gibco) for 20 selection of antibiotic resistant cells. Clonal CHO-K1 cell lines stably expressing HM74A were confirmed by [³⁵S]-GTPγS binding measurements, following the addition of nicotinic acid.

25 *P2 membrane preparation -* Plasma membrane-containing P2 particulate fractions were prepared from cell pastes frozen at -80°C after harvest. All procedures were carried out at 4°C. Cell pellets were resuspended in 1 ml of 10mM Tris-HCl and 0.1mM EDTA, pH 7.5 (buffer A) and by homogenisation for 20s with a Ultra Turrax followed by passage (5 times) through a 25-gauge needle. Cell lysates were centrifuged at 1,000g for 10 min in a microcentrifuge to pellet the nuclei and unbroken cells and P2 particulate fractions were 30 recovered by microcentrifugation at 16,000g for 30min. P2 particulate fractions were resuspended in buffer A and stored at -80°C until required.

35 *[³⁵S]-GTPγS binding -* assays were performed at room temperature in 384-well format based on methods described previously, (Wieland, T. and Jakobs, K.H. (1994) *Methods Enzymol.* 237, 3-13). Briefly, the dilution of standard or test compounds were prepared and added to a 384-well plate in a volume of 10µl. Membranes (HM74A or HM74) were diluted in assay buffer (20mM HEPES, 100mM NaCl, 10mM MgCl₂, pH7.4) supplemented with saponin (60µg/ml), Leadseeker WGA beads (Amersham; 250µg/well) and 10µM GDP, so that the 40 20µl volume added to each well contains 5µg of membranes. [³⁵S]-GTPγS (1170 Ci/mmol, Amersham) was diluted (1:1500) in assay buffer and 20µl added to each well. Following the addition of the radioligand, the plates were sealed, pulse spun and incubated for 4hours at room temperature. At the end of the incubation period the plates were read on a Leadseeker machine (VIEWLUX PLUS; Perkin-Elmer) to determine the levels of specific binding.

These assays were refined by reducing the final assay volume to 10 µl. For this 10 µl assay a revised protocol was used. This involved the use of only 100 nl of standard or test compound per well of a 384-well plate and 1.5 µg membrane and 100 µg Leadseeker WGA beads. For the low volume protocol, membrane, beads and [³⁵S]-GTPγS were mixed together and then 10 µl of this mix were dispensed to each well. Incubation and plate read were identical for the 10µl and 50 µl assays.

All exemplified compounds were tested in one or both of the [³⁵S]-GTPγS binding assays described above (i.e. the 10µl and 50µl assays).

Data was analysed by curve fitting as carried out using a Four Parameter Logistical equation using the XC50 software package (max 2 points deleted from any one curve). Specific binding is expressed as pEC₅₀ and as % efficacy compared to the maximal response of nicotinic acid binding.

In-vivo testing

HM74A agonists can be tested in male Spague-Dawley rats (200-250g) which have been fasted for at least 12 hours prior to the study. The compounds are dosed intravenously at either 1 or 3mg/kg (5ml/kg) or by oral gavage at doses ranging from 1-30mg/kg (10ml/kg). Blood samples (0.3ml tail vein bleed) can be taken pre-dose and at three times post-dose (times ranging from 15 minutes to 6 hours post-dose). Each blood sample is transferred to a heparin tube (Becton Dickinson Microtainer, PST LH) and centrifuged (10,000g for 5 minutes) to produce a plasma sample. The plasma samples are assayed for levels of non-esterified fatty acids (NEFA) using a commercially available kit (Randox). Inhibition of plasma NEFA levels, relative to pre-dose levels, are used as a surrogate for HM74A agonist activity.

In order to determine whether HM74A compounds exhibit the flushing response associated with nicotinic acid they can be dosed to conscious guinea-pigs. Male Dunkin Hartley guinea pigs (300-600g; n=10-20 per group) are fasted for at least 12 hours, but not in excess of 24 hours prior to experimentation. Pre-study blood samples (0.5ml) are taken from each animal by cardiac puncture under recovery anaesthesia (Isoflurane 3.5% with additional O₂ (1L/min)). Ear temperature measurements are taken by placing the left ear of each animal over an infra-red temperature probe. Measurements are taken at one minute intervals from 5 minutes pre-dose to 30 minutes post-dose. Temperature measurements are then taken at 15 minute intervals up to 2 hours post-dose. Animals receive test compounds by oral gavage (5ml/kg). Blood samples (0.5ml) are taken by cardiac puncture under terminal anaesthesia. Blood samples are taken from individual animals to provide data at 0.5, 1, 2, 3, and 4 hours post-dose. All blood samples are placed on a blood roller for 5 minutes then stored on ice until the end of the study. Following centrifugation (12000g for 5min) the

plasma is transferred into fresh tubes and stored at -20°C until assayed for NEFA concentrations.

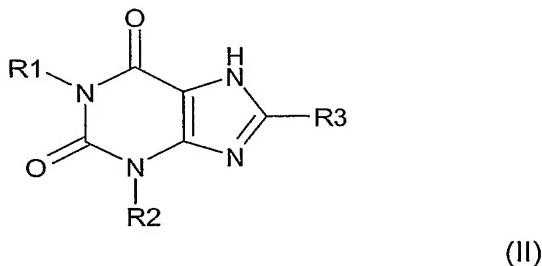
Compounds according to Formula (I) have been synthesised (see synthetic examples below)

5 and tested in the [35S]-GTPγS binding assays described above. All of the exemplified compounds have a pEC50 of 4.3 or greater and an efficacy of 30% or greater (in relation to nicotinic acid).

Compounds of Formula (I) may find use in human or veterinary medicine, in particular as
10 activators of HM74A, in the management of dyslipidaemia and hyperlipoproteinaemia.

According to another aspect of the invention there is provided the use of at least one
chemical entity selected from compounds of formula (II)

15



and pharmaceutically acceptable derivatives thereof, wherein

20

R¹ represents a group selected from: hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, and -(alk)_m-X-(alk)_n-Y,

25

Wherein X represents A, A1, A2 or a direct link;

A represents a group selected from:

cycloalkylene, cycloalkenylene, aryl, heteroaryl, heterocyclyl, -CH₂-OC(O)-;

30

A1 represents a group selected from:

-CH₂-O-(CH₂)_qaryl-O-, -CH₂-O-(CH₂)_wN(R⁵)C(O)O-, -CH₂-N(R⁵)C(O)O-, -CH₂-N(R⁵)C(O)-,
-CH₂-(O)_p-(CH₂)_qC(O)NR⁵-, -CH₂-N(R⁵)C(O)N(R⁵)-, -CH₂-C(O)N((CH₂)_wOH)-,
-CH₂-NR⁵-S(O)₂-; CH₂-S(O)₂NR⁵-, -CH₂-C(O)O-, -O-, -NR⁵-, -S-;

35

A2 represents:

-CH(OH)-;

When X is A, A1 or A2, Y represents a group selected from:

heteroaryl, heterocyclyl, aryl, cycloalkyl, cycloalkenyl, -O(CH₂)_n-aryl, -C(O)O-aryl, -CH(aryl)₂, -CH(heteroaryl)₂, -C₁₋₆ haloalkyl, -C(O)R⁴, -NR⁵R⁷, -C(O)NR⁵R⁷, -NR⁵C(O)R⁷, -NR⁵C(O)OR⁷, -C(O)(CH₂)_qOR⁴, halogen, cyano, -N(R⁵)C(O)OR⁷, -OC(O)NR⁵R⁶, -NR⁵C(O)R⁸, -OR⁵, -OC(O)R⁴;

5

When X is A1 and Y is selected from:

-O(CH₂)_n-aryl, -O-heteroaryl, -OR⁵, -OC(O)R⁵, -NH-aryl, -OC(O)NR⁵R⁶, n is an integer selected from 2, 3, 4 and 5;

10 When X is A1 and Y is -CF₃, or when X is A2, n is an integer selected from 1, 2, 3, 4 and 5;

When X is a direct link, Y represents a group selected from:

-C(O)(CH₂)_qOR⁵, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl, -heteroaryl, -heterocyclyl, -aryl, -cycloalkyl, -cycloalkenyl, -C₁₋₆ haloalkyl, -halo, -cyano, 3 or 4 ring fused system, -CH(aryl)₂, -CH(heteroaryl)₂, -OR⁵, -NR⁵R⁷, -NCOOR⁸, -(O)_pC(O)NR⁵R⁶, -NR⁵C(O)R⁸, -OR⁵, -(O)_pC(O)R⁴;

When Y incorporates a ring, that ring may be optionally substituted by one or more of:

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -NH₂, (CH₂)_q-NR⁵R⁷,

20 -(CH₂)_q-(O)_p-(CH₂)_q-N(R⁵)C(O)OR⁸, -(CH₂)_q-N(R⁵)C(O)R⁸, -(CH₂)_q-(O)_p-(CH₂)_q-C(O)NR⁵R⁶, -(CH₂)_q-N(R⁵)C(O)N(R⁵)R⁶, -(CH₂)_q-C(O)N((CH₂)_mOH)R⁵, -(CH₂)_q-N(R⁵)-S(O)₂R⁸, -CH₂-S(O)₂N(R⁵)R⁶, -C₁₋₆ haloalkyl, -OCF₃, -OCH(F)₂, -OCH₂F, -COOR⁵, -OR⁵, -(R⁸)_pCN, -S(O)₂R⁹, -(CH₂)_nheteroaryl, -(CH₂)_nheterocyclyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_naryl;

25

R² is selected from: hydrogen; or C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl, each of which may be optionally substituted by one or more of: C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C₁₋₆ haloalkyl, halogen, -CN, -OR⁴, -(CH₂)_nCOR⁴, -C(O)OR⁴, -OCOR⁴,

30 -(CH₂)_nNR⁵R⁶, -(NH)_pCONR⁵R⁶, -OCONR⁵R⁷, and -NHC(O)OR⁷;

R³ is selected from: S-C₁₋₆ alkyl, S-C₂₋₆ alkenyl, S-C₂₋₆ alkynyl, S-(CH₂)_nC₃₋₅ cycloalkyl, S-(CH₂)_nC₃₋₅ cycloalkenyl, S-(CH₂)_nC₃₋₅ heterocyclyl, S-(CH₂)_nC₅ aryl, S-(CH₂)_nC₅ heteroaryl;

35 R⁴ is selected from: hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_nheterocyclyl, -(CH₂)_naryl, and -(CH₂)_nheteroaryl;

R⁵ and R⁶ are selected from: hydrogen and C₁₋₄ alkyl;

40 R⁷ is selected from: hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_tcycloalkyl, -(CH₂)_tcycloalkenyl, -(CH₂)_theterocyclyl, -(CH₂)_taryl, and -(CH₂)_theteroaryl;

R⁸ is selected from C₁₋₄ alkyl;

45 R⁹ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_ncycloalkyl,

$-(CH_2)_n$ cycloalkenyl, $-(CH_2)_n$ heterocyclyl, $-(CH_2)_n$ aryl, and $-(CH_2)_n$ heteroaryl, CN;

m represents an integer selected from: 0, 1, 2, 3, 4 and 5;

5 n represents an integer selected from: 0, 1, 2, 3, 4 and 5;

p represents an integer selected from: 0 and 1;

q represents an integer selected from: 0, 1 and 2;

10 t represents an integer selected from: 1 and 2;

w represents an integer selected from: 2, 3 and 4.

15 in the manufacture of a medicament for the treatment of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia. In particular, the use is provided of a compound of Formula (II) in the manufacture of a medicament for the treatment of diabetic dyslipidaemia or mixed dyslipidaemia, heart failure, hypercholesterolaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, 20 coronary artery disease, thrombosis, angina, chronic renal failure, stroke and cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia.

In one embodiment of the present invention a compound of formula (I), (Ia) or (II) or a pharmaceutically acceptable derivative thereof, for use in human or veterinary medicine, 25 particularly in the treatment of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds are also provided for 30 use in the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

There is provided as a further aspect of the present invention a compound of formula (I), (Ia) or (II) or a pharmaceutically acceptable derivative thereof, for use in the manufacture of a 35 medicament for the treatment of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds are also provided for 40 use in the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

It will be appreciated that references herein to treatment extend to prophylaxis, prevention of recurrence and suppression of symptoms as well as the treatment of established conditions.

In one embodiment of the invention, there is provided a compound of formula (I), (Ia) or (II) for use in the treatment of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia. In particular, the use is provided of a compound of Formula (II) in the manufacture of a medicament for the treatment of diabetic dyslipidaemia or mixed dyslipidaemia, heart failure, hypercholesterolaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, stroke and cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia.

10 Additionally, the present invention provides the use of a compound of formula (I), (Ia) or (II) or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment of inflammatory diseases or conditions of the joint, particularly arthritis (e.g. rheumatoid arthritis, osteoarthritis, prosthetic joint failure), or of the gastrointestinal tract (e.g. ulcerative colitis, Crohn's disease, and other inflammatory bowel and gastrointestinal diseases, gastritis and mucosal inflammation resulting from infection, the enteropathy provoked by non-steroidal anti-inflammatory drugs), of the lung (e.g. adult respiratory distress syndrome, asthma, cystic fibrosis, or chronic obstructive pulmonary disease), of the heart (e.g. myocarditis), of nervous tissue (e.g. multiple sclerosis), of the pancreas, (e.g. inflammation associated with diabetes mellitus and complications thereof, of the kidney (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, eczema, urticaria, burn injury), of the eye (e.g. glaucoma) as well as of transplanted organs (e.g. rejection) and multi-organ diseases (e.g. systemic lupus erythematosus, sepsis) and inflammatory sequelae of viral or bacterial infections and inflammatory conditions associated with atherosclerosis and following hypoxic or ischaemic insults (with or without reperfusion), for example in the brain or in ischaemic heart disease.

In one embodiment, the compounds of formula (I), (Ia) or (II) or pharmaceutically acceptable derivatives thereof are useful in the treatment and prevention of inflammation, diabetes and cardiovascular diseases or conditions including atherosclerosis, arteriosclerosis, hypertriglyceridemia, and mixed dyslipidaemia.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with a condition where under-activation of the HM74A receptor contributes to the condition or where activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I), (Ia) or (II) or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment the present invention provides a method for the treatment of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, which method comprises administering to said human or animal subject an effective

amount of a compound of formula (I), (Ia) or (II) or a pharmaceutically acceptable derivative thereof. As such, these compounds may also find favour in methods for the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, which methods comprise administering to said human or animal subject an effective amount of a compound of formula (I), (Ia) or (II).

In one embodiment of formula (I) or (II), R¹ is selected from hydrogen C₁₋₁₀ alkyl, and -(alk)_m-X-(alk)_n-Y.

10 In one embodiment of formula (I) or (II), X represents A or A1. In a further embodiment of formula (I) or (II), A is selected from heteroaryl, heterocycll, and A1 is selected from CH₂-O-(CH₂)_wN(R⁵)C(O)O-, for example CH₂O(CH₂)₂NHC(O)O-, CH₂-N(R⁵)C(O)O- for example CH₂-NHC(O)O, CH₂-N(R⁵)C(O)- for example, CH₂-NHC(O)-, CH₂-(O)_p-(CH₂)_qC(O)NR⁵- for example CH₂C(O)NCH₃- , CH₂-N(R⁵)C(O)N(R⁵)- for example CH₂-NHC(O)NCH₃-,

15 CH₂-C(O)N((CH₂)_wOH)- for example CH₂-C(O)N((CH₂)₂OH)-, CH₂-NR⁵-S(O)₂- for example CH₂-NH-S(O)₂-, CH₂-S(O)₂NR⁵- for example CH₂-S(O)₂NCH₃-, and CH₂-C(O)O-. In another embodiment of formula (I) or (II), X represents A and A represents a heteroaryl. In another embodiment of formula (I) or (II), A represents a heteroaryl comprising a nitrogen heteroatom, for example, triazolyl, furazanyl, oxadiazolyl, tetrazolyl, imidazolyl or pyrazolyl.

20 In a further embodiment of formula (I) or (II), X represents A, for example heteroaryl or heterocycll, or a direct link.

25 In one embodiment of formula (I) or (II), Y represents an optionally substituted group selected from: aryl, for example phenyl or napthyl, heteroaryl, for example pyridinyl, thiazolyl, thienyl, benzofuranyl or indolyl, and O-aryl, for example O-phenyl.

30 In a further embodiment of formula (I) or (II), Y is substituted by one or more groups selected from OR⁵ for example OH or OCH₃, halogen, for example F or Cl, aryl, for example phenyl, C₁₋₆ haloalkyl for example CF₃ or CH₂CF₃ , OCF₃, (R⁸)_pCN for example CN, (CH₂)_q-N(R⁵)-S(O)₂R⁸ for example NHS(O)₂CH₃ and S(O)₂R⁹ for example S(O)₂CH₃.

35 In one embodiment of formula (I) or (II), when X represents A or A1, and A represents cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocycll, and A1 represents -CH₂-O-(CH₂)_wN(R⁵)C(O)O-, -CH₂-N(R⁵)C(O)O-, -CH₂-N(R⁵)C(O)-, -CH₂-(O)_p-(CH₂)_qC(O)NR⁵- , -CH₂-N(R⁵)C(O)N(R⁵)-, or -CH₂-C(O)N((CH₂)_wOH)-, and Y represents a ring, for example when X represents oxadiazolyl, tetrazolyl or pyrazolyl and Y represents phenyl, pyridinyl, or thienyl, m is an integer selected from 3 and 4 and n is an integer selected from 0 and 1, for example m is 4 and n is 0, or m is 3 and n is 1;

40 In one embodiment of formula (I), (Ia) or (II), R¹ is selected from: hydrogen; and C₁₋₁₀ alkyl which may be optionally substituted by one or more of: cycloalkyl, heterocycll, aryl, heteroaryl,

C₁₋₆ haloalkyl, halo, cyano, -OR⁴, -(CH₂)_nCOR⁴, -CO₂R⁴, -OCOR⁴, -(CH₂)_nNR⁵R⁷, and -(NH)_mCONR⁵R⁷. In another embodiment of formula (I), (Ia) or (II), R¹ is selected from: hydrogen; and C₁₋₁₀ alkyl which may be optionally substituted by one or more of: halo, cyano, -OR⁴, -(CH₂)_nCOR⁵, -CO₂R⁴, -OCOR⁴, -(CH₂)_nNR⁵R⁶, and -(NH)_mCONR⁵R⁶. In a further embodiment of formula (I), (Ia) or (II), R¹ is selected from: hydrogen and C₁₋₆ alkyl optionally substituted with -OH, for example methyl, butyl or CH₂CH₂OH.

In one embodiment of formula (I), (Ia), or (II), R¹ is selected from: hydrogen and C₁₋₆ alkyl, for example methyl or butyl.

10 In one embodiment of formula (I), (Ia) or (II), R² is selected from: C₄₋₁₀ alkyl and C₂₋₁₀ alkenyl, each of which may be optionally substituted by one or more of cycloalkyl, heterocycl, aryl, heteroaryl, C₁₋₆ haloalkyl, halo, cyano, -OR⁴, -(CH₂)_nCOR⁴, -CO₂R⁴, -OCOR⁴, -(CH₂)_nNR⁵R⁶, and -(NH)_mCONR⁵R⁶. In another embodiment of formula (I) (Ia) or (II), R² represents C₄₋₁₀ alkyl which may be optionally substituted by one or more of cycloalkyl, heterocycl, aryl, heteroaryl, C₁₋₆ haloalkyl, halo, cyano, -OR⁴, -(CH₂)_nCOR⁵, -CO₂R⁴, -OCOR⁴, -(CH₂)_nNR⁵R⁶, and -(NH)_mCONR⁵R⁶. In a further embodiment of formula (I) (Ia) or (II), R² is selected from C₄₋₆ alkyl, for example butyl or pentyl.

20 In one embodiment of formula (I), (Ia) or (II), R² represents C₁₋₁₀ alkyl which may be optionally substituted by one or more of: cycloalkyl, heterocycl, aryl, heteroaryl, C₁₋₆ haloalkyl, halogen, -CN, -OR⁴, -(CH₂)_nCOR⁵, -C(O)OR⁴, -OCOR⁴, -(CH₂)_nNR⁵R⁶, and -(NH)_pCONR⁵R⁶. In a further embodiment of formula (I), (Ia) or (II), R² is selected from C₃₋₆ alkyl, for example butyl or pentyl.

25 In one embodiment of formula (I) or (II), R³ is selected from: S-C₁₋₆ alkyl, C₃₋₅ cycloalkyl, S-(CH₂)_nC₃₋₅ cycloalkenyl, S-(CH₂)_nC₃₋₅ heterocycl, S-(CH₂)_nC₅ aryl, S-(CH₂)_nC₅ heteroaryl;

30 In one embodiment of formula (Ia), R³ is selected from: S-C₁₋₁₀alkyl, S-(CH₂)_ncycloalkyl, S-(CH₂)_nheterocycl, S-(CH₂)_n-aryl S-(CH₂)_nheteroaryl;

In one embodiment of formula (I), (Ia) or (II), R³ is selected from: S-C₁₋₄ alkyl, for example S-methyl or S-ethyl.

35 In one embodiment of formula (I), (Ia) or (II), R⁴ is selected from: hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_ncycloalkyl, -(CH₂)_nheterocycl, -(CH₂)_naryl, and -(CH₂)_nheteroaryl. In another embodiment of formula (I), (Ia) or (II) R⁴ is selected from: hydrogen and C₁₋₄ alkyl.

40 In one embodiment of formula (Ia) R¹ is selected from: hydrogen and C₁₋₆ alkyl, R² is selected from: C₄₋₆ alkyl and R³ is selected from S-C₁₋₄ alkyl and S-aryl.

In one embodiment of formula (I), (Ia) or (II), R¹ is selected from: hydrogen and C₁₋₆ alkyl, R² is selected from: C₄₋₆ alkyl and R³ is selected from: S-C₁₋₄ alkyl.

In a further embodiment of formula (I) or (II), it is provided that when X is A1, A1 is -O- and Y is a ring which is substituted by aryl or heteroaryl, then m is an integer selected from 3, 4 and 5.

In one embodiment of formula (I) or (II), R⁵ is hydrogen.

10 In one embodiment of formula (I) or (II), R⁷ is selected from: hydrogen and C₁₋₄ alkyl.

In one embodiment of formula (I) or (II), R¹ and R² are different.

15 It is to be understood that this aspect of the present invention includes any combination of particular embodiments and covers all combinations of particular substituents described herein above for compounds of Formula (I), (Ia) or (II).

Particular compounds of the present invention include:

1,3-Dibutyl-8-(methylthio)-3,7-dihydro-1H-purine-2,6-dione

20 8-(Methylthio)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione

8-(Methylthio)-3-pentyl-1-{3-[2-(phenylmethyl)-2H-tetrazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione

1-Methyl-8-(methylthio)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione

1,3-Dibutyl-8-(ethylthio)-3,7-dihydro-1H-purine-2,6-dione

25 The amount of a HM74A modulator which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the mode of administration and the precise clinical condition of the recipient. In general, the daily dose will be in the range of 0.1mg - 1g/kg, typically 0.1 - 100mg/kg. An intravenous dose may, for example, be in the range of 0.01mg to 0.1g/kg, typically 0.01mg to 10mg/kg, which may conveniently be administered as an infusion of from 0.1µg to 1mg, per minute. Infusion fluids suitable for this purpose may contain, for example, from 0.01µg to 0.1mg, per millilitre. Unit doses may contain, for example, from 0.01µg to 1g of a HM74A modulator. Thus ampoules for injection may contain, for example, from 0.01µg to 0.1g and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 0.1mg to 1g. No toxicological effects are indicated/expected when a compound of the invention is administered in the above mentioned dosage range.

40 A compound of the present invention may be employed as the compound *per se* in the treatment of a disease where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial, an example of this is where a compound of the present invention is presented with an acceptable carrier in the form of a pharmaceutical formulation. The carrier must, of course, be acceptable in the sense of

being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and may be formulated with the HM74A modulator as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the HM74A modulator.

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The formulations include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration.

There is also provided according to the invention a process for preparation of such a pharmaceutical composition which comprises mixing the ingredients.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges or tablets, each containing a predetermined amount of a HM74A modulator; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. In general, the formulations are prepared by uniformly and intimately admixing the active HM74A modulator with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or moulding a powder or granules of the HM74A modulator optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

25

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl α -hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a HM74A modulator in a flavoured base, usually sucrose and acacia or tragacanth, and pastilles comprising the HM74A modulator in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations for oral administration may be suitably formulated to give controlled/extended release of the active compound.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of an HM74A modulator, the formulation may be isotonic with the blood of the intended recipient. These preparations could be administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the HM74A modulator with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the HM74A modulator.

Thus, formulations of the present invention suitable for parenteral administration comprising a compound according to the invention may be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or toxicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

Formulations suitable for rectal administration may be presented as unit-dose suppositories. These may be prepared by admixing a HM74A modulator with one or more conventional solid carriers, for example, cocoa butter or glycerides and then shaping the resulting mixture.

Formulations suitable for topical application to the skin may take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The HM74A modulator is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include

ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

10

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

15

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

20

Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluorethane, carbon dioxide or other suitable gas.

25

Capsules and cartridges for use in an inhaler or insufflator, of for example gelatin, may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

30

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example in combination with other classes of dyslipidaemic drugs (e.g. statins, fibrates, bile-acid binding resins or nicotinic acid).

The compounds of the instant invention may be used in combination with one or more other therapeutic agents for example in combination with other classes of dyslipidaemic drugs e.g.

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3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) or fibrates or bile acid binding resins or nicotinic acid. The invention thus provides, in a further aspect, the use of such a combination in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial and the use of a compound of formula (I), (Ia) or (II), or a pharmaceutically acceptable salt,

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solvate or pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the combination therapy of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including

atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa or obesity.

When the compounds of the present invention are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above optimally together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When combined in the same formulation it will be appreciated that the two components must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately they may be provided in any convenient formulation, conveniently in such a manner as are known for such compounds in the art.

When in combination with a second therapeutic agent active against the same disease, the dose of each component may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or (Ia) or a pharmaceutically acceptable derivative thereof together with another therapeutically active agent.

The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent, excipient or carrier thereof represent a further aspect of the invention. For example, a pharmaceutical formulation comprising a compound or pharmaceutically acceptable derivative thereof and one or more pharmaceutically acceptable diluents, excipients or carriers.

35

General purification and analytical methods:

The mass spectra (MS) were recorded on a Fisons VG Platform mass spectrometer using electrospray positive ionisation [(ES+ve to give MH^+ and $M(NH_4)^+$ molecular ions] or electrospray negative ionisation [(ES-ve to give $(M-H)^-$ molecular ion] modes.

¹H NMR spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the external standard.

5 BiotageTM chromatography refers to purification carried out using equipment sold by Dyax Corporation (either the Flash 40i or Flash 150i) and cartridges pre-packed with KPSil.

10 Mass directed autoprep refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5µm column (5cm x 10mm i.d.) with 0.1% HCO₂H in water and 95% MeCN, 5% water (0.5% HCO₂H) utilising the following gradient elution conditions: 0-1.0 minutes 5%B, 1.0-8.0 minutes 5→30%B, 8.0-8.9 minutes 30%B, 8.9-9.0 minutes 30→95%B, 9.0-9.9 minutes 95%B, 9.9-10 minutes 95→0%B at a flow rate of 8ml minutes⁻¹ (System 2). The Gilson 202-fraction collector was triggered by a VG Platform Mass Spectrometer on detecting the mass of interest.

15 Preparative h.p.l.c. refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5µm column (10cm x 21.2mm i.d.) with 0.1% HCO₂H in water (A) and MeCN (0.5% HCO₂H) (B) utilising the generic gradient elution conditions expressed as "x to y" gradient with a gradient system as follows: 0-1.45minutes x%B, 1.45-20 minutes x→y%B, 20-24 minutes y→95%B, 24-30 minutes 95%B, 32-34 20 minutes 95→x%B at a flow rate of 8ml minutes⁻¹. The Gilson 233 fraction collector was triggered by UV (254nm).

25 SPE (solid phase extraction) refers to the use of cartridges sold by International Sorbent Technology Ltd.

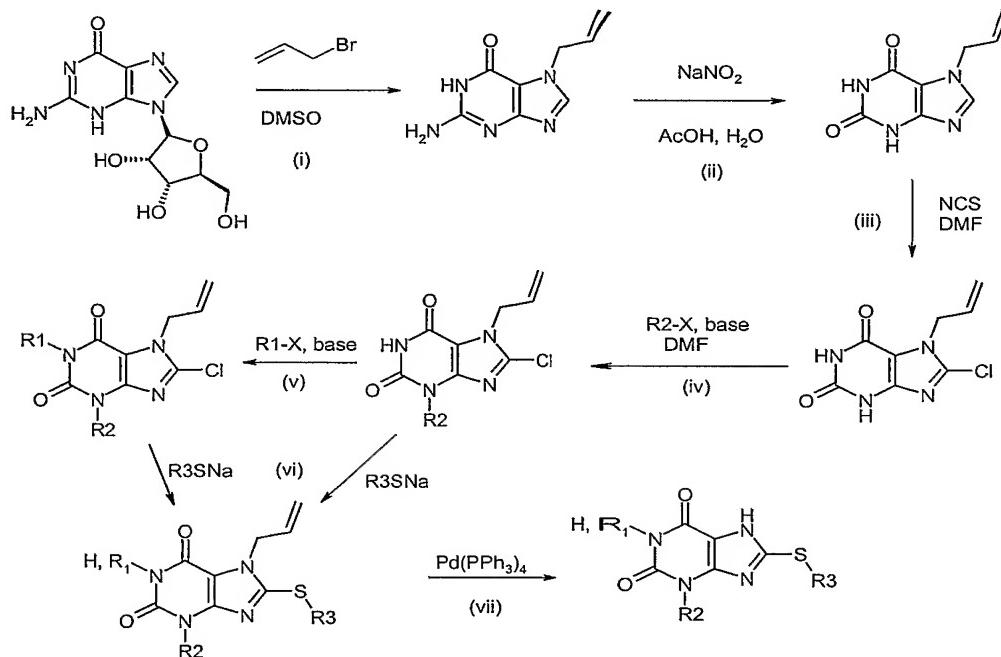
Strata Phenyl SPE refers to the use of cartridges sold by Phenomenex. The compound was loaded onto a cartridge previously conditioned with MeCN and equilibrated with 5% MeCN in water. The compound was eluted with 0.1% HCO₂H in water and MeCN (0.5% HCO₂H) in a suitable gradient on a CombiFlash Optix 10.

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35 The compounds of the present invention and pharmaceutically derivatives thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

Process A:

A process according to the invention for preparing a compound of formula (I) or formula (II) in which R¹ is H or alkyl and R² may be the same or different to R¹, comprises:



5 i) Alkylation

ii) Diazotisation followed by hydrolysis

iii) Chlorination

iv) Selective alkylation at N3 or dialkylation at N1 and N3

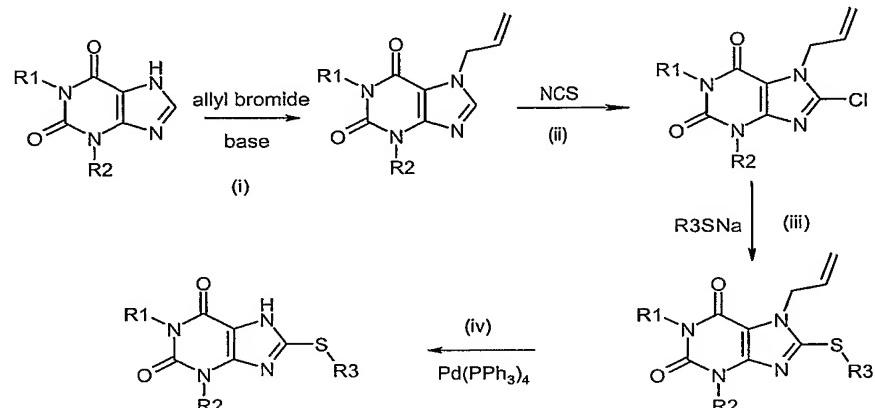
10 v) Alkylation at N1

vi) Displacement with thiolate

vii) Palladium mediated deprotection

Process B:

A process according to the invention for preparing a compound of formula (I) or formula (II) in which R¹ may be the same or different to R², comprises:



5 i) Alkylation

ii) Chlorination

iii) Displacement with thiolate

10 iv) Palladium mediated deprotection

Where desired or necessary, as a final stage in any of the above synthetic processes, a resultant compound of formula (I) or (II) can be converted into a pharmaceutically acceptable salt form or vice versa or converting one salt form into another pharmaceutically acceptable salt form.

ABBREVIATIONS

AcOH	Acetic acid
br	Broad (NMR)
CDI	Carbonyldiimidazole
d	Doublet (NMR)
DCM	Dichloromethane
DMSO	Dimethylsulfoxide
DMF	N,N-Dimethylformamide
EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour(s)
m	Multiplet (NMR)
MDAP	Mass directed autoprep
MeCN	Acetonitrile

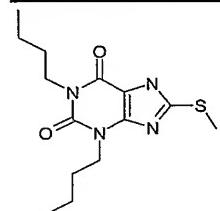
MeOH	Methanol
min	Minute(s)
NCS	N-Chlorosuccinimide
q	Quartet (NMR)
rt	Room temperature
RT	Retention time
s	Singlet (NMR)
SPE	Solid phase extraction cartridge
t	Triplet (NMR)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
DMEM	Dulbecco's Modified Eagle's Medium
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulphonic acid
LiHMDS	Lithium hexamethyldisilylamine

The following non-limiting examples illustrate the present invention:

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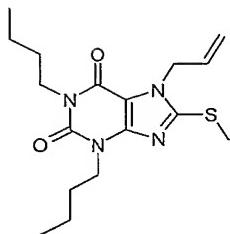
Synthetic Examples

Example 1: 1,3-Dibutyl-8-(methylthio)-3,7-dihydro-1*H*-purine-2,6-dione



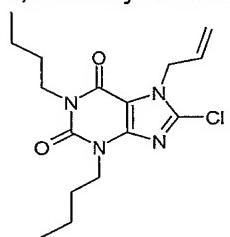
A mixture of 1,3-dibutyl-8-(methylthio)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.29mmol), Pd(PPh₃)₄ (66mg, 0.057mmol), PhSiH₃ (0.352ml, 2.85mmol) in AcOH (1.5ml) and DCM (3ml) was heated at 40°C for 18 hours. The reaction mixture was partitioned between 2M HCl(aq) and EtOAc. The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated. The residue was taken up in cyclohexane:DCM (1:1) and passed down an silica SPE (20g) cartridge eluting with EtOAc/cyclohexane mixtures (10%EtOAc/cyclohexane to 80%EtOAc/cyclohexane with increments of 10% EtOAc). The product fraction was concentrated, giving a yellow oil (219mg). The product was purified by mass directed hplc, giving a white solid (17mg, 19%). NMR δ_H (400MHz, d⁶-DMSO) 0.86-1.04 (m, 6H), 1.22-1.34 (m, 4H), 1.45-1.55 (m, 2H), 1.59-1.68 (m, 2H), 2.63 (s, 3H), 3.85 (t, 2H, J=7.5Hz), 3.95 (t, 2H, J=7Hz), 13.43 (br. s, 1H); m/z 311.3 [MH⁺].

1,3-dibutyl-8-(methylthio)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



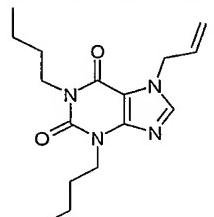
A solution of 1,3-dibutyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (600mg, 1.77mmol) in absolute EtOH (15ml) was treated with NaSMe (138mg, 1.97mmol) then heated at reflux for 4 hours. The mixture was allowed to cool then partitioned between 0.5M 5 HCl (aq) and EtOAc. The organic layer was separated and the aqueous extracted once again with EtOAc. The combined extracts were washed with brine, then dried (MgSO_4) and concentrated, giving a white solid (735mg, quant.). NMR δ_{H} (400MHz, CDCl_3) 0.90-1.00 (m, 6H), 1.35-1.44 (m, 4H), 1.57-1.67 (m, 2H), 1.70-1.79 (m, 2H), 2.70 (s, 3H), 3.98 (t, 2H, J=7.5Hz), 4.09 (t, 2H, J=7.5Hz), 4.87 (2H, d, J=6Hz), 5.18 (d, 1H, J=17Hz), 5.25 (d, 1H, J=10.5Hz), 5.90-6.02 (m, 1H).

1,3-dibutyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 1,3-dibutyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.6g, 5.3mmol) 15 in anhydrous DMF (10ml) was treated with NCS (774mg, 5.8mmol). The reaction was left to stir at rt. under nitrogen for 18 hours. The mixture was partitioned between EtOAc and sat. NaHCO_3 (aq) solution. The organic layer was separated, washed with 2M HCl(aq), brine, then dried (MgSO_4) and concentrated, giving a pale yellow oil (1.74g). The title compound was purified by passing the oil through an SPE(20g) cartridge eluting with 20 EtOAc/cyclohexane mixtures and concentrating product fractions. Gave a white solid (1.37g, 77%). NMR; (400MHz, $d^6\text{-DMSO}$) δ_{H} 0.86 (2xt overlapping, 6H), 1.28 (m, 4H), 1.50 (m, 2H), 1.62 (m, 2H), 3.84 (t, 2H, 7=Hz), 3.92 (t, 2H, J=7Hz), 4.91 (br. d, 2H, J=5Hz), 5.01 (br. dd, 1H, J=17Hz & 1Hz), 5.21 (br. dd, 1H, J=10Hz & 1Hz), 5.97 (m, 1H). m/z 339 [MH^+].

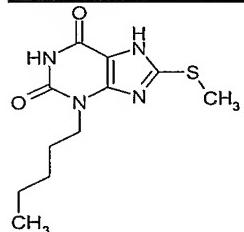
25 1,3-dibutyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 1,3-di-N-butylxanthine (10g, 0.038mol) in anhydrous DMF (80ml) was first treated with K_2CO_3 (5.2g, 0.038mol) and then allyl bromide (3.6ml, 0.042mol). The mixture

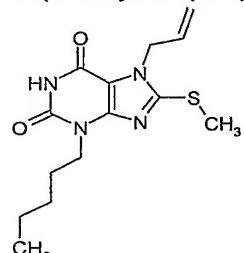
was heated at 55°C for 18 hours. After cooling to rt. the mixture was partitioned between water (+a small quantity of 2M HCl(aq)) and EtOAc. The organic layer was separated and the aqueous was extracted once more with EtOAc. The combined extracts were washed with brine, dried (MgSO_4) and concentrated, giving an off-white solid (16.5g). The solid was taken up into 30% EtOAc/cyclohexane and passed through a silica column eluting with the same solvent mixture. The product fractions were combined and concentrated which gave the title compound as a white solid after drying under high vacuum at 60°C for 2 hours. (12.2g, quant.) NMR; δ_{H} (400MHz, d^6 -DMSO) δ_{H} 0.88 (2xt overlapping, 6H), 1.27 (septet, 4H, $J=7\text{Hz}$), 1.49 (quintet, 2H, $J=8\text{Hz}$), 1.62 (quintet, 2H, $J=8\text{Hz}$), 3.84 (t, 2H, $J=7\text{Hz}$), 3.96 (t, 2H, $J=7\text{Hz}$), 4.88 (d, 2H, $J=6\text{Hz}$), 5.10 (d, 1H, $J=17\text{Hz}$), 5.19 (d, 1H, $J=10\text{Hz}$), 6.05 (m, 1H), 8.06 (s, 1H). m/z 305 [MH^+].

Example 2: 8-(Methylthio)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

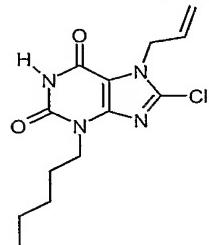


15 8-(methylthio)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (53mg, 0.17mmol) was taken up into AcOH (1ml) and DCM (3ml) then sequentially treated with $\text{Pd}(\text{PPh}_3)_4$ (40mg, 0.034mmol) and PhSiH_3 (212 μl , 1.7mmol). The mixture was degassed by applying a gentle vacuum and then nitrogen introduced. The solution was stirred at rt. for 17 hours and then it was partitioned between 2M HCl(aq) and EtOAc. The organic layer was separated, washed with brine, dried (MgSO_4) and concentrated. The title compound was purified by autoprep hplc, giving a white solid (5mg). NMR; (400MHz, d^6 -DMSO) δ_{H} 0.85 (t, 3H, $J=7\text{Hz}$), 1.20-1.36 (m, 4H), 1.63 (quintet, 2H, $J=7\text{Hz}$), 2.61 (3H, s), 3.87 (2H, t, $J=7\text{Hz}$), 10.90 (1H, br. s). m/z 269 [MH^+].

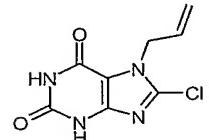
25 8-(methylthio)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



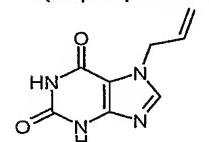
A solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.34mmol) in anhydrous EtOH (3ml) was treated with fresh NaSMe (100mg, 0.37mmol) and heated at reflux for 18 hours. The mixture was allowed to cool then partitioned between 0.5M HCl(aq) and EtOAc. The organic layer was separated and washed with brine, dried (MgSO_4) and concentrated. The product was purified by SPE (10g) column eluting with cyclohexane and EtOAc mixtures. The product fractions were concentrated giving the title compound (53mg). m/z 309.1 [MH^+].

8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione

To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.44mmol) in anhydrous DMF (3ml) was added sodium carbonate (0.051g, 0.484mmol). After 10 minutes stirring at room temperature pentyl iodide (0.063ml, 0.484mmol) was added and stirring continued under nitrogen at room temperature for 18 hours. The reaction mixture was diluted with water (25ml) and extracted with EtOAc (2x25ml). The combined organic extracts were dried (MgSO_4) filtered and evaporated. Purification by SPE (Si, 5g) eluting with 4:1 EtOAc/cyclohexane afforded the title compound as a white solid (96mg, 74%); m/z 297.2[MH⁺].

8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione

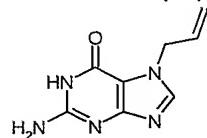
To a solution of 7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (10.52g, 54.7mmol) in anhydrous DMF (60ml) was added NCS (8.04g, 60.2mmol). The reaction mixture was left to stir under nitrogen at 20°C for 6 hours. The reaction mixture was concentrated *in vacuo* to give an amber oil. MeOH was added and left to stand for 18 hours. The resulting residue was filtered and dried under vacuum to give the title compound (7.69g, 62%). m/z 227.2[MH⁺].

7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione

A mixture of 2-amino-7-(2-propen-1-yl)-1,7-dihydro-6*H*-purin-6-one (40g, 0.209mol) in AcOH (900ml) and water (100ml) was heated at 55°C. Sodium nitrite (57.74g, 0.837mol) in water (100ml) was added dropwise. Care; toxic fumes. After the addition was complete (ca. 25 minutes) the reaction mixture was allowed to cool to ambient temperature and then concentrated to ca. 1/3 of its original volume. Water (500ml) was added and the resulting precipitate collected by filtration. The residue was washed with water then dried at 50°C over P_2O_5 and under vacuum for 2 hours to give the title compound (17.20g). The aqueous fraction was concentrated and water added (100ml). Again the resulting solid was filtered

and dried. This gave more of the title compound (2.31g). Combined product (19.52g, 49%). m/z 193.2[MH⁺].

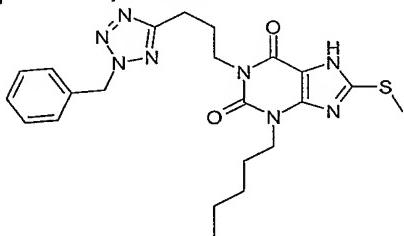
2-amino-7-(2-propen-1-yl)-1,7-dihydro-6H-purin-6-one



A mixture of guanosine (20g, 0.071 mol), allyl bromide (14.7ml, 0.169mol) and anhydrous DMSO (100ml) was stirred at rt, under nitrogen, for 18 hours. Conc. HCl (50ml of 37%) was added in one portion and the mixture stirred for 45 minutes then poured into MeOH (600ml). The methanolic solution was neutralised with 2M NaOH(aq) solution and the resulting white precipitate collected by filtration. The white solid was dried under vacuum at 50°C for 18 hours to afford the title compound (16g crude, 119%). m/z 192.2[MH⁺].

Example 3: 8-(Methylthio)-3-pentyl-1-{3-[2-(phenylmethyl)-2H-tetrazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione

a) 8-(Methylthio)-3-pentyl-1-{3-[2-(phenylmethyl)-2H-tetrazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione



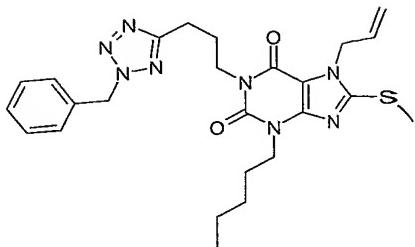
To a solution of 8-(methylthio)-3-pentyl-1-{3-[2-(phenylmethyl)-2H-tetrazol-5-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.12g, 0.23mmol) in dichloromethane (4ml) was added acetic acid (1.5ml) and phenylsilane (0.35ml). The solution was de-oxygenated (successive application of vacuum and introduction of nitrogen) and Pd(PPh₃)₄ (0.075g) added. The solution was heated at 42°C for 7h, allowed to cool and then concentrated.

Chromatography (20g silica SPE) eluting with dichloromethane/cyclohexane 2:1 to remove fast moving by-products then dichloromethane followed by gradient elution of dichloromethane/ether 9:1 to pure ether to provide 8mg of title compound contaminated with an impurity. The product was further purified by MDAP to yield 1.5mg, 1% of the title compound as a white solid.

LC/MS: m/z 469 [MH]⁺, RT 3.48min.

¹H NMR (CDCl₃) δ: 0.9 (t, 3H, J = 7Hz), 1.38 (m, 4H), 1.76 (m, 2H), 2.45 (m, 2H), 2.68 (s, 3H), 4.1 (t, 2H, J = 7Hz), 4.2 (s, 2H), 4.25 (t, 2H, J = 7Hz), 4.68 (t, 2H, J = 7Hz), 7.3 (m, 5H).

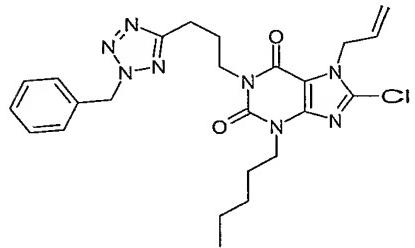
b) 8-(Methylthio)-3-pentyl-1-{3-[2-(phenylmethyl)-2H-tetrazol-5-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione



To a solution of 8-chloro-3-pentyl-1-{3-[2-(phenylmethyl)-2H-tetrazol-5-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.144g, 0.29mmol) in THF (5ml) was added sodium thiomethoxide (0.061g, 0.9mmol). The solution was stirred for 36h then quenched with ethyl acetate/water. The organics were isolated, dried ($MgSO_4$) and concentrated. The crude was purified by chromatography (10g silica SPE) eluting with a gradient of dichloromethane to dichloromethane/ether 9:1 to provide the title compound as clear oil (0.127g, 86%).

LC/MS: m/z 509 [MH]⁺, RT 3.85min.

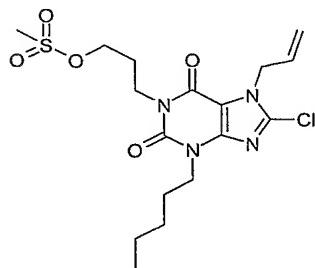
c) 8-Chloro-3-pentyl-1-{3-[2-(phenylmethyl)-2H-tetrazol-5-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione



To a solution of 3-[8-chloro-2,6-dioxo-3-pentyl-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1H-purin-1-yl]propyl methanesulfonate (0.6g, 1.4mmol) in DMF (15ml) was added benzyl tetrazole (0.22g, 1.4mmol) followed by potassium carbonate (0.38g, 2.8mmol). The mixture was stirred for 2h at ambient then at 70°C for 18h then cooled. In an attempt to displace the 8-chloro group *in situ* sodium thiomethoxide (0.10g, 1.4mmol) was added to the solution and the mixture stirred for 18h. LCMS of the reaction showed largely 8-chloro-3-pentyl-1-{3-[2-(phenylmethyl)-2H-tetrazol-5-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione present therefore the reaction was diluted with ethyl acetate and washed with brine. The organic fraction was isolated, dried and concentrated. The crude was chromatographed (20g silica SPE) gradient elution with dichloromethane/cyclohexane 3:2 to pure dichloromethane then to dichloromethane/ethyl acetate 3:1 yield 8-chloro-3-pentyl-1-{3-[2-(phenylmethyl)-2H-tetrazol-5-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.32g, 46%) followed by 8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1H-tetrazol-5-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.093g, 13%).

LC/MS: m/z 497 [MH]⁺, RT 3.73min.

d) 3-[8-Chloro-2,6-dioxo-3-pentyl-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate



5 To a solution of 8-chloro-1-(3-hydroxypropyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.62g, 1.75mmol) in dichloromethane (15ml) was added triethylamine (0.24ml, 1.75mmol) followed by the portion wise addition of mesyl anhydride (0.30g, 1.75mmol) over 5min. The solution was stirred for 1h then separated between dichloromethane and water. The organics were washed with sodium bicarbonate solution, dried and concentrated to yield the title compound as a clear oil (0.60g, 79%), which was used without further purification.

10 LC/MS: m/z 433 [MH]⁺, RT 3.33min.

e) 8-Chloro-1-(3-hydroxypropyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione

15

To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.72g, 2.4mmol) and 3-bromo-1-propanol (0.65ml, 4.8mmol) in DMF (20ml) was added potassium carbonate (0.67g, 4.8mmol) and the mixture stirred for 18h after which time it was diluted with water and extracted with ethyl acetate. The organic fraction was washed with brine, dried and concentrated. The crude product was purified over silica (20g SPE), gradient elution with dichloromethane/cyclohexane 2:1 to dichloromethane then to dichloromethane/ethyl acetate 4:1 to provide the title compound as a clear oil (0.83g, 96%).

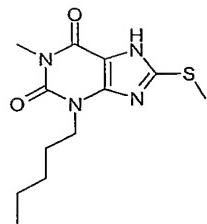
20

25 LC/MS: m/z 355 [MH]⁺, RT 3.05min.

Example 4: 1-Methyl-8-(methylthio)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

30

a) 1-Methyl-8-(methylthio)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

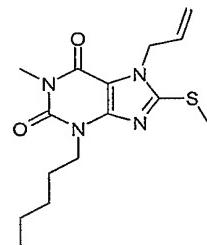


To a degassed solution (by application of sequentially vacuum and nitrogen) of 1-methyl-8-(methylthio)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.066g, 0.21mmol) in dichloromethane (2ml)/acetic acid (1ml) was added Pd(PPh₃)₄ (0.047g, 0.041mmol). After 5 degassing further, phenylsilane (0.25ml, 2.05mmol) was added and the solution stirred for 3h. The mixture was partitioned between EtOAc and dilute hydrochloric acid and the organic fraction separated, washed with brine and dried (MgSO₄). Concentration *in vacuo* followed by purification over silica (SPE) using a gradient elution (cyclohexane/ethyl acetate 0-50%) provided the title compound contaminated with catalyst residues. This material was further 10 purified using MDAP to provide the title compound (1.7mg, 3%)

LC/MS: m/z 283 [MH]⁺, RT 2.99min.

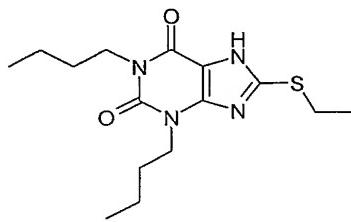
¹H NMR (CDCl₃) δ_H: 0.9 (t, 3H, J = 7Hz), 1.35 (m, 4H), 1.76 (m, 2H), 2.75 (s, 3H), 3.45 (s, 3H), 4.1 (t, 2H, J = 7Hz).

15 b) 1-Methyl-8-(methylthio)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 8-chloro-1-methyl-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.10g, 0.32mmol) in DMF (3ml) was treated with sodium thiometoxide (0.025g, 0.35mmol) and the solution heated to 80°C for 3days. The solution was partitioned between ethyl acetate and dilute hydrochloric acid. The organics were separated, washed with brine, dried (MgSO₄) and concentrated to provide the title compound as a clear oil. LC/MS: m/z 323 20 [MH]⁺, RT 3.49min.

25 **Example 5: 1,3-Dibutyl-8-(ethylthio)-3,7-dihydro-1*H*-purine-2,6-dione**



A solution of 1,3-dibutyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.30mmol) in EtOH (3ml) was treated with NaSEt (28mg, 0.33mmol) and heated at reflux for 4h. Another portion of NaSEt (28mg, 0.33mmol) was added and heated at reflux for a further 18h. The mixture was partitioned between EtOAc and water. A small amount of 2M HCl(aq) was added to aid separation. The organic layer was separated washed with brine, dried (MgSO_4) and concentrated. DCM (2ml) and AcOH (1ml) were added and the mixture degassed under gentle vacuum, then nitrogen introduced. Pd(PPh_3)₄ (58mg) was added and the degassing cycle repeated. PhSiH₃ (0.31ml) was added and the mixture stirred at rt. for 3h after which a portion of Pd(PPh_3)₄ (58mg) was added and left to stir for a further 18h. The mixture was partitioned between EtOAc and water. A small amount of 2M HCl(aq) was added to aid separation. The organic layer was separated, washed with brine, dried (MgSO_4) and concentrated. Purification by first aminopropyl SPE and then preparative LC provided the title compound (7mg).

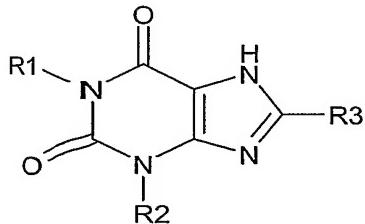
LC/MS m/z 325 [MH⁺], RT 3.5mins.

¹H NMR; (d^6 -DMSO) δ_{H} 0.89 (6H, m), 1.30 (7H, m), 1.50 (2H, m), 1.64 (2H, m), 3.19 (2H, q, *J* = 7Hz), 3.85 (2H, t, *J* = 7Hz), 3.96 (2H, t, *J* = 7Hz), 13.5 (1H, br s).

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Claims

1. At least one chemical entity selected from compounds of formula (I)



(I)

5

and pharmaceutically acceptable derivatives thereof, wherein

R^1 represents a group selected from: hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and
10 $-(alk)_m-X-(alk)_n-Y$,

Wherein X represents A, A1, A2 or a direct link;

A represents a group selected from:

15 cycloalkylene, cycloalkenylene, aryl, heteroaryl, heterocyclyl, $-CH_2-OC(O)-$;

A1 represents a group selected from:

$-CH_2-O-(CH_2)_q-Aryl-O-$, $-CH_2-O-(CH_2)_wN(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)-$,
10 $-CH_2-(O)_p-(CH_2)_qC(O)NR^5-$, $-CH_2-N(R^5)C(O)N(R^5)-$, $-CH_2-C(O)N((CH_2)_wOH)-$,
20 $-CH_2-NR^5-S(O)_2-$, $CH_2-S(O)_2NR^5-$, $-CH_2-C(O)O-$, $-O-$, $-NR^5-$, $-S-$;

A2 represents:

$-CH(OH)-$;

25 When X is A, A1 or A2, Y represents a group selected from:

heteroaryl, heterocyclyl, aryl, cycloalkyl, cycloalkenyl, $-O(CH_2)_n-Aryl$, $-C(O)O-Aryl$, $-CH(Aryl)_2$,
- $CH(heteroaryl)_2$, $-C_{1-6}haloalkyl$, $-C(O)R^4$, $-NR^5R^7$, $-C(O)NR^5R^7$, $-NR^5C(O)R^7$, $-NR^5C(O)OR^7$,
- $C(O)(CH_2)_qOR^4$, halogen, cyano, $-N(R^5)C(O)OR^7$, $-OC(O)NR^5R^6$, $-NR^5C(O)R^8$, $-OR^5$,
- $OC(O)R^4$;

30

When X is A1 and Y is selected from:

$-O(CH_2)_n-Aryl$, $-O-heteroaryl$, $-OR^5$, $-OC(O)R^5$, $-NH-Aryl$, $-OC(O)NR^5R^6$,
n is an integer selected from 2, 3, 4 and 5;

35 When X is A1 and Y is $-CF_3$, or when X is A2, n is an integer selected from 1, 2, 3, 4 and 5;

When X is a direct link, Y represents a group selected from:

-C(O)(CH₂)_qOR⁵, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl, -heteroaryl, -heterocyclyl, -aryl, -cycloalkyl, -cycloalkenyl, -C₁₋₆haloalkyl, -halo, -cyano, 3 or 4 ring fused system, -CH(aryl)₂, -CH(heteroaryl)₂, -OR⁵, -NR⁵R⁷, -NCOOR⁸, -(O)_pC(O)NR⁵R⁶, -NR⁵C(O)R⁸, -OR⁵, -(O)_pC(O)R⁴;

5

When Y incorporates a ring, that ring may be optionally substituted by one or more of:

C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halogen, -NH₂, (CH₂)_q-NR⁵R⁷, -(CH₂)_q-(O)_p-(CH₂)_q-N(R⁵)C(O)OR⁸, -(CH₂)_q-N(R⁵)C(O)R⁸, -(CH₂)_q-(O)_p-(CH₂)_q-C(O)NR⁵R⁶, -(CH₂)_q-N(R⁵)C(O)N(R⁵)R⁶, -(CH₂)_q-C(O)N((CH₂)_mOH)R⁵, -(CH₂)_q-N(R⁵)-S(O)₂R⁸, -CH₂-S(O)₂N(R⁵)R⁶, -C₁₋₆haloalkyl, -OCF₃, -OCH(F)₂, -OCH₂F, -COOR⁵, -OR⁵, -(R⁸)_pCN, -S(O)₂R⁹, -(CH₂)_nheteroaryl, -(CH₂)_nheterocyclyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_naryl;

10

R² is selected from: hydrogen; or C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl, each of which may be optionally substituted by one or more of: C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C₁₋₆haloalkyl, halogen, -CN, -OR⁴, -(CH₂)_nCOR⁴, -C(O)OR⁴, -OCOR⁴, -(CH₂)_nNR⁵R⁶, -(NH)_pCONR⁵R⁶, -OCONR⁵R⁷, and -NHC(O)OR⁷;

20

R³ is selected from: S-C₁₋₆alkyl, S-C₂₋₆alkenyl, S-C₂₋₆alkynyl, S-(CH₂)_nC₃₋₅cycloalkyl, S-(CH₂)_nC₃₋₅cycloalkenyl, S-(CH₂)_nC₃₋₅heterocyclyl, S-(CH₂)_nC₅aryl, S-(CH₂)_nC₅heteroaryl;

25

R⁴ is selected from: hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_nheterocyclyl, -(CH₂)_naryl, and -(CH₂)_nheteroaryl;

R⁵ and R⁶ are selected from: hydrogen and C₁₋₄alkyl;

30

R⁷ is selected from: hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -(CH₂)_tcycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_theterocyclyl, -(CH₂)_taryl, and -(CH₂)_theteroaryl;

R⁸ is selected from C₁₋₄alkyl;

35

R⁹ is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_nheterocyclyl, -(CH₂)_naryl, and -(CH₂)_nheteroaryl, CN;

m represents an integer selected from: 0, 1, 2, 3, 4 and 5;

40

n represents an integer selected from: 0, 1, 2, 3, 4 and 5;

p represents an integer selected from: 0 and 1;

q represents an integer selected from: 0, 1 and 2;

45

t represents an integer selected from: 1 and 2;

w represents an integer selected from: 2, 3 and 4;

with the proviso that:

- i) when R¹ and R² represent ethyl, R³ is other than SMe; and
- ii) when R¹ represents ethyl or n-propyl and R² represents n-propyl, R³ is other than SBu-n.

5

2. At least one chemical entity according to claim 1 wherein R¹ is selected from: hydrogen C₁₋₁₀ alkyl, and -(alk)_m-X-(alk)_n-Y.

10

3. At least one chemical entity according to claim 1 or 2 wherein X represents A or a direct link.

4. At least one chemical entity according to claim 1 or 2 wherein R¹ is selected from: hydrogen and C₁₋₆ alkyl.

15

5. At least one chemical entity according to any preceding claim wherein R² is selected from: C₄₋₆ alkyl.

6. At least one chemical entity according to any preceding claim wherein R³ is selected from: S-C₁₋₄ alkyl.

20

7. At least one chemical entity according to any preceding claim for use in human or veterinary medicine.

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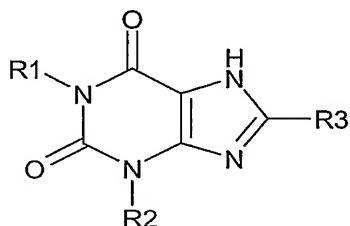
8. At least one chemical entity according to any one of claims 1-6, for use in the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia and/or of inflammatory diseases or conditions.

30

9. At least one chemical entity according to any one of claims 1-6 for use in the treatment of diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease or stroke.

35

10. At least one chemical entity selected from compounds of formula (II)



(II)

and pharmaceutically acceptable derivatives thereof, wherein

R¹ represents a group selected from: hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, and -(alk)_m-X-(alk)_n-Y,

5 Wherein X represents A, A1, A2 or a direct link;

A represents a group selected from:

cycloalkylene, cycloalkenylene, aryl, heteroaryl, heterocyclyl, -CH₂-OC(O)-;

10 A1 represents a group selected from:

-CH₂-O-(CH₂)_qaryl-O-, -CH₂-O-(CH₂)_wN(R⁵)C(O)O-, -CH₂-N(R⁵)C(O)O-, -CH₂-N(R⁵)C(O)-, -CH₂-(O)_p-(CH₂)_qC(O)NR⁵-, -CH₂-N(R⁵)C(O)N(R⁵)-, -CH₂-C(O)N((CH₂)_wOH)-, -CH₂-NR⁵-S(O)₂-, CH₂-S(O)₂NR⁵-, -CH₂-C(O)O-, -O-, -NR⁵-, -S-;

15 A2 represents:

-CH(OH)-;

When X is A, A1 or A2, Y represents a group selected from:

heteroaryl, heterocyclyl, aryl, cycloalkyl, cycloalkenyl, -O(CH₂)_n-aryl, -C(O)O-aryl, -CH(aryl)₂,

20 -CH(heteroaryl)₂, -C₁₋₆ haloalkyl, -C(O)R⁴, -NR⁵R⁷, -C(O)NR⁵R⁷, -NR⁵C(O)R⁷, -NR⁵C(O)OR⁷, -C(O)(CH₂)_qOR⁴, halogen, cyano, -N(R⁵)C(O)OR⁷, -OC(O)NR⁵R⁶, -NR⁵C(O)R⁸, -OR⁵, -OC(O)R⁴;

When X is A1 and Y is selected from:

25 -O(CH₂)_n-aryl, -O-heteroaryl, -OR⁵, -OC(O)R⁵, -NH-aryl, -OC(O)NR⁵R⁶, n is an integer selected from 2, 3, 4 and 5;

When X is A1 and Y is -CF₃, or when X is A2, n is an integer selected from 1, 2, 3, 4 and 5;

30 When X is a direct link, Y represents a group selected from:

-C(O)(CH₂)_qOR⁵, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl, -heteroaryl, -heterocyclyl, -aryl, -cycloalkyl, -cycloalkenyl, -C₁₋₆ haloalkyl, -halo, -cyano, 3 or 4 ring fused system, -CH(aryl)₂, -CH(heteroaryl)₂, -OR⁵, -NR⁵R⁷, -NCOOR⁸, -(O)_pC(O)NR⁵R⁶, -NR⁵C(O)R⁸, -OR⁵, -(O)_pC(O)R⁴;

35

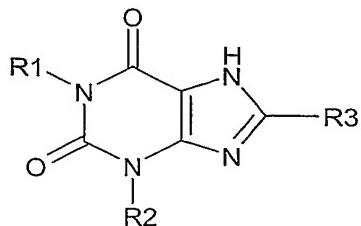
When Y incorporates a ring, that ring may be optionally substituted by one or more of:

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -NH₂, (CH₂)_q-NR⁵R⁷,

-(CH₂)_q-(O)_p-(CH₂)_q-N(R⁵)C(O)OR⁸, -(CH₂)_q-N(R⁵)C(O)R⁸, -(CH₂)_q-(O)_p-(CH₂)_q-C(O)NR⁵R⁶, -(CH₂)_q-N(R⁵)C(O)N(R⁵)R⁶, -(CH₂)_q-C(O)N((CH₂)_wOH)R⁵, -(CH₂)_q-N(R⁵)-S(O)₂R⁸,

40 -CH₂-S(O)₂N(R⁵)R⁶, -C₁₋₆ haloalkyl, -OCF₃, -OCH(F)₂, -OCH₂F, -COOR⁵, -OR⁵, -(R⁸)_pCN, -S(O)₂R⁹, -(CH₂)_nheteroaryl, -(CH₂)_nheterocyclyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_naryl;

- 5 R² is selected from: hydrogen; or C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, cycloalkenyl, heterocycl, aryl, and heteroaryl, each of which may be optionally substituted by one or more of: C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, heterocycl, aryl, heteroaryl, C₁₋₆ haloalkyl, halogen, -CN, -OR⁴, -(CH₂)_nCOR⁴, -C(O)OR⁴, -OCOR⁴, -(CH₂)_nNR⁵R⁶, -(NH)_pCONR⁵R⁶, -OCONR⁵R⁷, and -NHC(O)OR⁷;
- 10 R³ is selected from: S-C₁₋₆ alkyl, S-C₂₋₆ alkenyl, S-C₂₋₆alkynyl, S-(CH₂)_nC₃₋₅ cycloalkyl, S-(CH₂)_nC₃₋₅ cycloalkenyl, S-(CH₂)_nC₃₋₅ heterocycl, S-(CH₂)_nC₅ aryl. S-(CH₂)_nC₅ heteroaryl;
- 15 R⁴ is selected from: hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_nheterocycl, -(CH₂)_naryl, and -(CH₂)_nheteroaryl;
- 20 R⁵ and R⁶ are selected from: hydrogen and C₁₋₄ alkyl;
- 25 R⁷ is selected from: hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_tcycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_theterocycl, -(CH₂)_taryl, and -(CH₂)_theteroaryl;
- 30 R⁸ is selected from C₁₋₄ alkyl;
- 35 R⁹ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_nheterocycl, -(CH₂)_naryl, and -(CH₂)_nheteroaryl, CN;
- m represents an integer selected from: 0, 1, 2, 3, 4 and 5;
- n represents an integer selected from: 0, 1, 2, 3, 4 and 5;
- p represents an integer selected from: 0 and 1;
- q represents an integer selected from: 0, 1 and 2;
- t represents an integer selected from: 1 and 2;
- w represents an integer selected from: 2, 3 and 4;
- for use in the manufacture of a medicament for treating diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure or stroke.
- 40 11. A method for the treatment of a human or animal subject having a condition where under-activation of the HM74A receptor contributes to the condition or where activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of at least one chemical entity selected from compounds of formula (II)
- 45



(II)

and pharmaceutically acceptable derivatives thereof, wherein

5 R¹ represents a group selected from: hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, and -(alk)_m-X-(alk)_n-Y,

Wherein X represents A, A1, A2 or a direct link;

10 A represents a group selected from:

cycloalkylene, cycloalkenylene, aryl, heteroaryl, heterocyclyl, -CH₂-OC(O)-;

A1 represents a group selected from:

-CH₂-O-(CH₂)_qaryl-O-, -CH₂-O-(CH₂)_wN(R⁵)C(O)O-, -CH₂-N(R⁵)C(O)O-, -CH₂-N(R⁵)C(O)-,

15 -CH₂-(O)_p-(CH₂)_qC(O)NR⁵-, -CH₂-N(R⁵)C(O)N(R⁵)-, -CH₂-C(O)N((CH₂)_wOH)-,

-CH₂-NR⁵-S(O)₂-, CH₂-S(O)₂NR⁵-, -CH₂-C(O)O-, -O-, -NR⁵-, -S-;

A2 represents:

-CH(OH)-;

20 When X is A, A1 or A2, Y represents a group selected from:
heteroaryl, heterocyclyl, aryl, cycloalkyl, cycloalkenyl, -O(CH₂)_n-aryl, -C(O)O-aryl, -CH(aryl)₂,

-CH(heteroaryl)₂, -C₁₋₆ haloalkyl, -C(O)R⁴, -NR⁵R⁷, -C(O)NR⁵R⁷, -NR⁵C(O)R⁷, -NR⁵C(O)OR⁷,
-C(O)(CH₂)_qOR⁴, halogen, cyano, -N(R⁵)C(O)OR⁷, -OC(O)NR⁵R⁶, -NR⁵C(O)R⁸, -OR⁵,
-OC(O)R⁴;

When X is A1 and Y is selected from:

-O(CH₂)_n-aryl, -O-heteroaryl, -OR⁵, -OC(O)R⁵, -NH-aryl, -OC(O)NR⁵R⁶,

n is an integer selected from 2, 3, 4 and 5;

30 When X is A1 and Y is -CF₃, or when X is A2, n is an integer selected from 1, 2, 3, 4 and 5;

When X is a direct link, Y represents a group selected from:

-C(O)(CH₂)_qOR⁵, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl, -heteroaryl, -heterocyclyl,
35 -aryl, -cycloalkyl, -cycloalkenyl, -C₁₋₆ haloalkyl, -halo, -cyano, 3 or 4 ring fused system,
-CH(aryl)₂, -CH(heteroaryl)₂, -OR⁵, -NR⁵R⁷, -NCOOR⁸, -(O)_pC(O)NR⁵R⁶, -NR⁵C(O)R⁸, -OR⁵,
-(O)_pC(O)R⁴;

When Y incorporates a ring, that ring may be optionally substituted by one or more of:

40 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -NH₂, (CH₂)_q-NR⁵R⁷,
-(CH₂)_q-(O)_p-(CH₂)_q-N(R⁵)C(O)OR⁸, -(CH₂)_q-N(R⁵)C(O)R⁸, -(CH₂)_q-(O)_p-(CH₂)_q-C(O)NR⁵R⁶,
-(CH₂)_q-N(R⁵)C(O)N(R⁵)R⁶, -(CH₂)_q-C(O)N((CH₂)_wOH)R⁵, -(CH₂)_q-N(R⁵)-S(O)₂R⁸,
-CH₂-S(O)₂N(R⁵)R⁶, -C₁₋₆ haloalkyl, -OCF₃, -OCH(F)₂, -OCH₂F, -COOR⁵, -OR⁵,
-(R⁸)_pCN, -S(O)₂R⁹, -(CH₂)_nheteroaryl, -(CH₂)_nheterocyclyl, -(CH₂)_ncycloalkyl,

$-(CH_2)_n$ cycloalkenyl, $-(CH_2)_n$ aryl;

R^2 is selected from: hydrogen; or C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl, each of which may be optionally substituted by one or more of: C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C₁₋₆ haloalkyl, halogen, -CN, -OR⁴, -(CH₂)_nCOR⁴, -C(O)OR⁴, -OCOR⁴, -(CH₂)_nNR⁵R⁶, -(NH)_pCONR⁵R⁶, -OCONR⁵R⁷, and -NHC(O)OR⁷;

R^3 is selected from: S-C₁₋₆ alkyl, S-C₂₋₆ alkenyl, S-C₂₋₆ alkynyl, S-(CH₂)_nC₃₋₅ cycloalkyl, S-(CH₂)_nC₃₋₅ cycloalkenyl, S-(CH₂)_nC₃₋₅ heterocyclyl, S-(CH₂)_nC₅ aryl, S-(CH₂)_nC₅ heteroaryl;

R^4 is selected from: hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_nheterocyclyl, -(CH₂)_naryl, and -(CH₂)_nheteroaryl;

R^5 and R^6 are selected from: hydrogen and C₁₋₄ alkyl;

R^7 is selected from: hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_tcycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_theterocyclyl, -(CH₂)_taryl, and -(CH₂)_theteroaryl;

R^8 is selected from C₁₋₄ alkyl;

R^9 is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_nheterocyclyl, -(CH₂)_naryl, and -(CH₂)_nheteroaryl, CN;

m represents an integer selected from: 0, 1, 2, 3, 4 and 5;

n represents an integer selected from: 0, 1, 2, 3, 4 and 5;

p represents an integer selected from: 0 and 1;

q represents an integer selected from: 0, 1 and 2;

t represents an integer selected from: 1 and 2;

w represents an integer selected from: 2, 3 and 4.

12. A method according to claim 11 wherein the human or animal subject has a disorder of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia or an inflammatory disease or condition.

13. A pharmaceutical formulation comprising at least one chemical entity according to any one of claims 1-6 and one or more pharmaceutically acceptable diluents, excipients or carriers.

14. A combination for administration together or separately, sequentially or simultaneously in separate or combined pharmaceutical formulations, said combination comprising at least one chemical entity according to any one of claims 1-6 together with another therapeutically active agent.

15. A pharmaceutical formulation comprising:

- (i) At least one chemical entity according to any one of claims 1-6;
- (ii) one or more active ingredients selected from statins, fibrates, bile-acid binding resins
5 and nicotinic acid; and
- (iii) one or more pharmaceutically acceptable diluents, excipients or carriers.

INTERNATIONAL SEARCH REPORT

International application No
101/EP2005/O11374

A. CLASSIFICATION OF SUBJECT MATTER
C07D473/06 C07D473/04 A61K31/522 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIAGI, GIULIANA ET AL: "2-Alkyloxyalkylthiohypoxanthines as new potent inhibitors of xanthine oxidase" FARMACO , 56(11), 809-813 CODEN: FRMCE8; ISSN: 0014-827X , 2001, XP002363909 compound 12	1,2,4, 6-14
X	BRUNS R F: "ADENOSINE ANTAGONISM BY PURINES, PTERIDINES AND BENZOPTERIDINES IN HUMAN FIBROBLASTS" BIOCHEMICAL PHARMACOLOGY, PERGAMON, OXFORD, GB, vol. 30, no. 4, 1981, pages 325-333, XP002108789 ISSN: 0006-2952 Table 1, A13, A23, A24	1,2,4, 7-14

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

31 January 2006

Date of mailing of the international search report

09/02/2006

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INTERNATIONAL SEARCH REPORT

International application No

/EP2005/011374

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 62 175483 A (SUNTORY LTD) 1 August 1987 (1987-08-01) Formula 1f; example 7 -----	1,2,4, 7-10,13, 14
X	RAM, VISHNU J. ET AL: "Purine analogs as potential chemotherapeutic agents. III" JOURNAL OF HETEROCYCLIC CHEMISTRY , 19(1), 153-5 CODEN: JHTCAD; ISSN: 0022-152X, 1982, XP002363911 compounds 2, 3d -----	1,2,4, 7-10,13, 14
X	ROMEROA, ANTONIO ET AL: "Palladium phosphine complexes from 8-(thio)theophylline, 8-(methylthio)theophylline and 8-(benzylthio)theophylline" INORGANICA CHIMICA ACTA , 307(1-2), 125-130 CODEN: ICHAA3; ISSN: 0020-1693, 2000, XP002363908 Scheme 1 -----	1,2,4,6
X	PARHAM, JAMES C. ET AL: "Competitive reactivity of nitrenium and carbenium ion contributors of purinium cations with "soft" bases" JOURNAL OF ORGANIC CHEMISTRY , 47(4), 652-7 CODEN: JOCEAH; ISSN: 0022-3263, 1982, XP002363910 page 657, 8-(phenylthio)xanthine -----	1,2,4
X	RO 104 611 B1 (INSTITUTUL DE MEDICINA SI FARMACIE, IASI) 29 August 1994 (1994-08-29) the whole document -----	1,2,4
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KRASOVSKII, A. N. ET AL: "Synthesis and some properties of S-propargyl and S-acetonitrile derivatives of azoles" XP002363916 retrieved from STN Database accession no. 1978:152568 compound IV abstract & KHIMIKO-FARMATSEVTICHESKII ZHURNAL , 12(1), 72-6 CODEN: KHFZAN; ISSN: 0023-1134, 1978, -----	1,2,4

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INTERNATIONAL SEARCH REPORT

I ational application No
EP2005/011374

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REICHMAN, URI ET AL: "Alkaline hydrolysis of methylthiopurines bearing oxo groups in the ring" JOURNAL OF ORGANIC CHEMISTRY , 38(19), 3367-71 CODEN: JOCEAH; ISSN: 0022-3263, 1973, XP002363912 Compounds 5,6 -----	1,2,4
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; WEILER-FEILCHENFELD, H. ET AL: "Fine structure of purines" XP002363917 retrieved from STN Database accession no. 1971:517662 8-(decylthio)-theophylline abstract & QUANTUM ASPECTS HETEROCYCL. COMPOUNDS CHEM. BIOCHEM., PROC. INT. SYMP., 2ND , MEETING DATE 1969, 308-13. EDITOR(S): BERGMANN, ERNST D. PUBLISHER: ISRAEL ACAD. SCI. HUM., JERUSALEM, ISRAEL. CODEN: 23ULAG, 1970, -----	1,2,4,6
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CACACE, FULVIO ET AL: "Derivatives of 8-mercaptopatheophylline: synthesis of a thiazolidino'2',3'-7,8!theophylline" XP002363918 retrieved from STN Database accession no. 1957:34894 8-(allylthio)-theophylline abstract & ANNALI DI CHIMICA (ROME, ITALY) , 46, 806-11 CODEN: ANCRAI; ISSN: 0003-4592, 1956, -----	1,2,4
X	LISTER, JOHN H.: "Purine studies. XXI. Benzyl group translocations in 9-benzylxanthine derivatives" AUSTRALIAN JOURNAL OF CHEMISTRY , 32(2), 387-97 CODEN: AJCHAS; ISSN: 0004-9425, 1979, XP008058835 8-benzylthio-1-methylxanthine; 8-benzylthio-3-methylxanthine page 396 -----	1,2,4,6
	-/-	

INTERNATIONAL SEARCH REPORT

International application No
.../EP2005/011374

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STOEHRRER, GERHARD ET AL: "Oncogenic purine derivatives: evidence for a possible proximate oncogen" SCIENCE (WASHINGTON, DC, UNITED STATES) , 167, 1622-4 CODEN: SCIEAS; ISSN: 0036-8075, 1970, XP008058837 compound 5 -----	1,2,4,6
X	BILTZ, HEINRICH ET AL: "Alkylation in the xanthine series" JOURNAL FUER PRAKTISCHE CHEMIE (LEIPZIG) , 118, 198-221 CODEN: JPCEAO; ISSN: 0021-8383, 1928, XP008058836 8-(ethylthio)-xanthine; 8-(ethylthio)-theophylline page 213 - page 214 -----	1,2,4,6
A	WO 02/084298 A (GLAXO GROUP LIMITED; FOORD, STEVEN, MICHAEL; PIKE, NICHOLAS, BRIAN; WI) 24 October 2002 (2002-10-24) cited in the application the whole document -----	1-14
A	EP 0 430 300 A (TAKEDA CHEMICAL INDUSTRIES, LTD) 5 June 1991 (1991-06-05) Table 1a, no 23,24; page 38, formula (II) -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/011374

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11,12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
/EP2005/011374

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
JP 62175483	A	01-08-1987	NONE		
RO 104611	B1	29-08-1994	NONE		
WO 02084298	A	24-10-2002	EP 1377834 A2 US 2004254224 A1		07-01-2004 16-12-2004
EP 0430300	A	05-06-1991	CA 2031328 A1		02-06-1991